14 Lithium

Essential Concepts

- Lithium is a very well proven treatment for pure mania and for bipolar depression, both acutely and in prophylaxis.
- It is the most proven psychotropic medication, of any kind for any condition, for the prevention of suicide and the prolongation of life.
- The main medical risks of lithium are hypothyroidism, which is usually treatable and reversible, and renal impairment.
- Severe, irreversible renal impairment with lithium is rare and is associated with long-term effects of past acute toxicity as well as multiple daily dosing.
- Lithium appears to have neuroprotective effects.
- Lithium should not be stopped abruptly, except in the setting of acute toxicity.
- Sudden discontinuation markedly increases the risk of acute mania within 1 month.
- Lithium generally should be dosed once daily to minimize long-term renal impairment and to enhance compliance.

INDICATIONS

Lithium is the only treatment for acute mania approved by the Food and Drug Administration (FDA). However, there are sufficient controlled data to support its use in the maintenance prophylaxis of bipolar disorder. Some controlled data also exist for its use in acute depression occurring in bipolar disorder and as an augmentation of antidepressants in the treatment of unipolar major depressive disorder.

PHARMACOLOGY

Lithium is a naturally occurring medication. The standard lithium formulation is lithium carbonate. Other lithium formulations are lithium citrate, which can be better tolerated than the carbonate compound in the setting of severe nausea, and Eskalith CR, a controlled-release type of lithium. Eskalith leads to lower serum peaks of lithium and may be associated with fewer cognitive side effects, such as poor concentration or sedation; however, it may be associated with more renal side effects.

The usual dosage of lithium is around 900 to 1,200 mg per day (range 600 to 1,500 mg per day). It often is given two or three times daily, but it can be given in a one-time dose because its mean half-life is about 24 hours. It is dosed to a serum therapeutic range of 0.6 to 1.2 ng/dL, somewhat lower in the elderly (0.4 to 0.8 ng/dL). A standard level for acute and maintenance treatment is 0.8 ng/dL (0.4 ng/dL in the elderly). Lithium is not metabolized in the liver and is excreted unchanged by the kidney. Thus its only drug interactions involve other medications that can affect its renal excretion.

MECHANISMS OF ACTION

For many years, the mechanism of action of lithium was unknown. Lithium has mildly proserotonergic effects, but it does not significantly affect other major neurotransmitters (such as dopamine or norepinephrine). Recent data strongly indicate that lithium's main effects do not occur at the synapse with neurotransmitters but postsynaptically, at the level of G-proteins and other second messengers [such as phosphatidylinositol phosphate (PIP)]. It is these cellular effects that probably mediate lithium's clinical utility.

Specifically, lithium inhibits the alpha unit of G-proteins, especially those connected to beta-adrenergic receptors via cyclic adenosine monophosphate (cAMP). By blocking the G-protein transmission of messages from these noradrenergic receptors, lithium may interfere with the neuronal activity that occurs with mania. Similar effects on G-proteins linked to other neurotransmitters may produce lithium's antidepressant effects. Furthermore, lithium may inhibit PIP function when PIP is excessively active, but lithium has no effect when PIP is normally active. Thus, by its complex second-messenger functions, lithium essentially may be reestablishing intracellular homeostases that underlie larger neural circuits subserving mood, accounting for its mood-stabilizing effects.

DOSING AND LABORATORY TESTS

Lithium should be dosed only once daily because it has a half-life of 24 hours. The common practice of dosing lithium multiple times daily is based on habit without any general rationale. In some cases, if lithium is dosed all at once, a patient may experience some sedation or cognitive impairment. In such cases, more than once-daily dosing may be necessary. Dosing lithium at night minimizes such side effects. Another option is to use slow-release lithium (such as Lithobid or Eskalith), which minimizes the peak-blood-level side effects. Slow-release formulations also may lead to somewhat less impairment of urinary concentrating capacity. It is my practice to use generic lithium carbonate, all given at night, and then to move to Eskalith or Lithobid if side effects seem excessive. If gastrointestinal effects predominate, the liquid lithium citrate formulation may be best tolerated.

It is advisable to check thyroid and kidney function tests before beginning lithium, within 1 week of initiation, 1 month later, 3 months later, and then every 6 to 12 months in maintenance treatment. I check lithium levels and the other tests one to three times in the first 1 to 2 months of treatment to be certain of therapeutic levels and also to rule out acute antithyroid effects. When checking for thyroid function, I always check free T_4 levels in addition to thyroid-stimulating hormone (TSH) owing to the potential for subclinical hypothyroidism, in which free T_4 levels are low or low-normal and TSH levels can be normal.

SIDE EFFECTS AND TOXICITY

Lithium has four groups of side effects: nuisance, medically serious, toxic, and teratogenic. Nuisance side effects occur at therapeutic levels and lower, are often related to noncompliance, and are experienced as troublesome. These include sedation, cognitive difficulties such as poor concentration and memory, a sense of decreased creativity, dry mouth, hand tremor, increased appetite, weight gain, increased fluid intake (polydipsia), increased urination (polyuria), nausea, diarrhea, psoriasis, and acne. Polydipsia and polyuria persist in about 25% of patients during maintenance treatment with lithium. When severe, this increased urination may represent nephrogenic diabetes insipidus, a condition due to lithium's inhibition of the kidney's sensitivity to the pituitary's antidiuretic hormone (ADH, or vasopressin).

Some of these side effects are treatable. Sedation and cognitive effects may improve with the controlled-release formulation; dry mouth can be minimized by use of sugar-free candy; increased appetite and weight gain can be responsive to carbohydrate restriction (since lithium has a mild insulin-like effect) and exercise; nausea and diarrhea may respond to the citrate formulation; hand tremor may improve with the use of propanolol; and polydipsia/polyuria can improve with the use of thiazide diuretics such as the hydrochlorothiazide-triamterene combination. Since thiazide diuretics increase lithium levels, lithium doses should be decreased by about 50% in coadminstration and levels followed. It should be noted that because of lithium's mild insulin-like effect, the insulin regimen of diabetic patients receiving lithium also may need to be altered. Frequently, despite these measures, individuals are unable to tolerate lithium solely owing to these nuisance side effects, which are the main source of lithium noncompliance (Table 14.1).

Medically serious side effects (excluding toxicity) fall into three subcategories: thyroid abnormalities, chronic renal insufficiency, and cardiac effects. Lithium's thyroid effects can occur early in treatment but often appear after years of use as well. Lithium has a direct reversible antithyroid effect, and thus it can lead to hypothyroidism (usually in about 5% of patients). It inhibits the thyroid gland's sensitivity to TSH. High TSH levels on laboratory tests indicate a need to either discontinue lithium or supplement it with thyroid hormone replacement. Either T_4 or T_3 formulations can be used, alone or in combination; the most common practice is to use T_4 (L-thyroxine) because it is metabolized in the body to T_3 naturally.

Lithium's kidney effect is more long term, usually seen after 10 to 20 years of chronic therapy. Unlike the acute direct inhibition of renal concentrating ability (including diabetes insipidus), this long-term effect of lithium is often irreversible and may involve renal glomerular function, resulting in a mild azotemia in most cases (mildly elevated creatinine

TABLE 14.1. Causes of Lithium Noncompliance

1. Nuisance side effects
2. Multiple daily dosing
3. Stigma
4. Missing highs
5. Lack of insight

levels). Lithium appears to reduce glomerular filtration rate, usually slightly. In rare instances, it can lead to severe chronic renal insufficiency and nephrotic syndrome, with glomerular pathologies of varying types. In the setting of new azotemia, the clinician needs to consider switching from lithium to another agent, although sometimes lithium can be continued safely as long as future kidney function tests do not worsen beyond mild abnormalities.

Lithium's cardiac effects mainly consist of some decrease in cardiac conduction efficiency, which can result in sick sinus syndrome. Lithium can produce blockade of the sinoatrial node, premature ventricular beats, and atrioventricular blockade. If lithium use is essential in a patient with these effects, a cardiac pacemaker may be necessary. Otherwise, the use of a different mood stabilizer may be indicated.

It is noteworthy that lithium mildly increases free calcium levels, possibly by stimulating direct release of parathyroid hormone from the pituitary gland, but this effect has little clinical significance, and hypercalcemia is not a serious problem. Lithium also can produce a mild leukocytosis, although this as well is without clinical sequelae.

Lithium toxicity occurs in nonelderly adults usually beginning at a level of 1.2 ng/dL (Table 14.2), with minimal side effects of tremor, nausea, diarrhea, and ataxia. Levels from 1.5 to 2.0 ng/dL are associated with a higher risk of seizures. Above 2.0 ng/dL, acute renal failure can occur, and dialysis may be warranted. Above 2.5 ng/dL, coma and death can occur, and dialysis is indicated. In the elderly, these signs of toxicity can occur at half these levels. A special warning is appropriate for the elderly depressed patient who experiences diminished appetite: Decreased fluid intake will raise lithium levels to toxic ranges quickly. If renal failure is produced, lithium levels rise exponentially, greatly increasing the risk of death. Thus dialysis is essential in such patients.

TABLE 14.2. Lithium Levels

<0.4 ng/dL	Probably no psychotropic effect; possible long-term cognitive or antisuicide benefits
0.4–0.6 ng/dL	Ineffective for bipolar disorder type I usually; may be therapeutic level in the elderly; possibly effective in bipolar disorder type II
0.6–1.0 ng/dL	Effective in bipolar disorder type I (whether acute or maintenance treatment); ideal level is 0.8 ng/dL; may be toxic in the elderly
1.0–1.2 ng/dL	Not proven more effective than lower levels in bipolar disorder type I; increased risk of toxicity with dehydration
1.2–1.5 ng/dL	Borderline toxicity in adults (increased tremor, polyuria, possible confusion); fully toxic in the elderly
1.5–2.0 ng/dL	Toxic; risk of seizures; should be discontinued and levels monitored
>2.0 ng/dL	Consider dialysis; risk of acute renal failure
>2.5 ng/dL	Potentially fatal; risk of coma

Early reports based on retrospective data found that lithium was associated with increased levels of congenital cardiac malformations in children of mothers treated during pregnancy. Specifically, Ebstein's anomaly, a malformation of the tricuspid valve, was associated with lithium use in the first trimester of pregnancy. Recent prospective studies report lower risks than in the past. However, cardiac malformations, specifically Ebstein's anomaly, are still generally thought to be a risk with lithium use during pregnancy. These risks are probably lower than the risks of neural tube defects associated with the use of anticonvulsant mood stabilizers such as divalproex and carbamazepine in pregnancy. Thus, in the severely ill manic patient who requires treatment, lithium use, with or without high-potency conventional antipsychotics, at times may be necessary, ideally after the first trimester of pregnancy. However, if possible, lithium use is still generally avoided during pregnancy.

CLINICAL BENEFITS

Lithium is quite effective in pure mania (i.e., euphoric mood) but less effective than the anticonvulsants in mixed (depressive, dysphoric) mania. It is by far the agent most well proven in the prevention of mood episodes, of both depression and mania, in bipolar disorder. A number of common misconceptions need to be addressed. First, it is often held that anticonvulsants are more effective than lithium in the treatment of rapid cycling; yet head-to-head studies indicate that both carbamazepine and divalpreox are similar to lithium in that difficult-to-treat population. Further, lamotrigine has been shown twice to be equivalent to placebo in patients with rapid cycling. Second, it is commonly thought that lamotrigine is more effective than lithium in the prevention of bipolar depressive episodes. Yet those studies only included patients

who responded initially to lamotrigine, and thus they were not fairly designed to compare lamotrigine and lithium. Third and similarly, one study compared olanzapine with lithium in patients who responded initially to olanzapine for acute mania, with the observation of better prevention of mania with olanzapine than with lithium. Again, this study is biased in favor of olanzapine owing to its enrichment design and thus does not allow for a meaningful claim of superiority over lithium. Fourth, recent FDA indications for maintenance treatment with some antipsychotics (e.g., olanzapine and aripiprazole) are based on only one placebo-controlled, randomized study with each drug. In the case of lamotrigine, two such randomized maintenance studies exist. In all these cases, the studies were conducted solely by the drugs' corporate sponsors. In contrast, lithium maintenance studies have been conducted over five decades by numerous independent research groups and number in the thirties (although many of them are relatively small). Hence the amount of evidence supporting lithium's efficacy far exceeds that of the other agents.

In both treatment of acute bipolar depression and prevention of bipolar depressive episodes, antidepressants [both tricyclic antidepressants (TCAs) and serotonin reuptake inhibitors (SRIs)] have been shown repeatedly to be no better than lithium, and sometimes worse.

Further, in refractory unipolar depression, lithium is the most proven effective adjunctive treatment in randomized studies, although it is worth keeping in mind that most of these studies were conducted in the pre-DSM-IV era and thus likely included patients with bipolar disorder type II.

Lithium is the psychotropic agent best proven to reduce mortality in any psychiatric illness, with evidence of reduction in death from suicide as well as from cardiovascular disease. Recently, evidence is also emerging that lithium has neuroprotective effects by promoting various neurotrophic factors, which may lead to protection from long-term cognitive impairment as a result of the deleterious physiologic effects of repeated mood episodes.

CLINICAL WEAKNESSES

It has been demonstrated that lithium response is lower in patients with rapid cycling, psychotic features, or substance abuse (compared with not having those states). However, such patients generally are treatment-refractory, and contrary to common opinion, anticonvulsants have not been shown to be more effective than lithium in such states. The only condition in which anticonvulsants have clearly been shown to be more effective than lithium is the mixed episode.

LITHIUM WITHDRAWAL SYNDROME

It is important to recognize that lithium should not be discontinued abruptly (except in a medically dangerous case of acute lithium toxicity). If it is stopped suddenly, there is a 50% risk of sudden mania within 1 month, as well as some evidence of a marked increased short-term risk of suicide. If tapered over 2 weeks or longer, those risks appear to subside. Thus lithium generally should be tapered at that speed; often a reduction of 300 mg per week is sufficient.

CONVINCING DOCTORS TO PRESCRIBE LITHIUM

Despite the preceding discussion, it is my experience that psychiatrists are often hesitant to prescribe lithium. Older psychiatrists may have had bad experiences in the past, when, in the absence of viable alternatives, lithium was often dosed at higher blood levels than currently proven in the search for better response (often leading to toxicity). Younger psychiatrists are simply unfamiliar with how to use it.

The best view may be what Frederick Goodwin expressed when he said, "If you can't use lithium, or won't use lithium, get out of the business of treating bipolar disorder." When the most effective and most proven treatment is put aside, then, as doctors, we are not advocating for the best care of our patients.

For those doctors concerned about medical toxicities and risks and the need for laboratory monitoring, my view is that they need to remember that they are medical doctors; it is acceptable to use medications that have medical risks, and it is necessary to have enough medical knowledge to be able to assess and follow those risks. Otherwise, (like psychologists), nonphysicians would be right in their claims that they should be allowed to prescribe medications.

For doctors worried that patients might overdose or that poor medical outcomes may occur, it is important always to weigh the risks of any drug against its benefits. Simply to look for low-risk drugs, without weighing benefits, ultimately

shortchanges patients. Yes, lithium has risks, but its benefits far outweigh those of its competitors as well.

CONVINCING PATIENTS TO TAKE LITHIUM

Sometimes the doctor is willing, but the patient is not. Often this reluctance has to do with the fact that lithium has long been associated with the diagnosis of manic-depressive illness and thus may carry more stigma than newfangled drugs. In other cases, patients may have taken lithium in the past, often in the hospital, with many side effects. In my experience, the latter scenario usually involves high blood levels of lithium combined with polypharmacy with hefty doses of antipsychotics or other agents. I always try to reason with my patients that they may not have side effects with lithium alone, especially if it is titrated very gradually.

In the case of stigma, I remind my patients that bipolar disorder is bipolar disorder, and the choice of medication does not increase or decrease the severity of the illness. I then recite the benefits of lithium, especially the mortality and cognitive benefits, which are almost always unknown to patients, and then I find them more open to lithium.

Finally, for patients especially attracted to natural treatments, such as herbal medications, owing to their being found in nature and not synthetic, I remind them that lithium is a mineral found in rocks and is part of the table of chemical elements. It is hard to get more natural than that.

Standard Anticonvulsants

Essential Concepts

- Valproate generally is well tolerated, although it can cause gastrointestinal and cognitive side effects, as well as weight gain.
- Despite causing weight gain, valproate does not appear to cause the metabolic syndrome and, in fact, seems to have some beneficial lipid effects.
- Carbamazepine is the only standard mood stabilizer with a low risk of weight gain (unlike lithium and valproate).
- Carbemazepine can be difficult to use owing to its many drug interactions.
- Both agents are indicated by the Food and Drug Administration (FDA) for the treatment of acute mania.
- For mixed episodes, they are more effective than lithium or lamotrigine.
- Both agents have reasonable evidence of efficacy in prevention of mood episodes in bipolar disorder and thus can be considered to be mood stabilizers.
- Both agents have small but replicated evidence of efficacy for acute bipolar depression. This benefit is less well proven than with lithium or quetiapine but more well proven than with lamotrigine or olanzapine.

VALPROATE

Indications

Valproate is indicated by the FDA for the treatment of acute mania. A number of studies have shown it to be at least equivalent to lithium or better than placebo, and there are also controlled data indicating that valproate is superior to lithium in treating the acute mixed episode.